REMARKS

I. Status of the Claims

Claims 1, 6-8, 12, and 21-34 are pending in this application. All pending claims stand rejected.

II. Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Claim 22 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter. In the Amendment dated July 21, 2010, Applicant amended claim 22 to add the full name "cyclophosphamide oncovin daunomycin prednione l-asparaginase" for the abbreviation "CODPL" But the Office maintains the rejection, and requires Applicant provide prior art or a reference to prove that CODPL is known in the art to represent the full name added to claim 22.

Applicant encloses herein an Information Disclosure Statement ("IDS") including a document available as of February 24, 2005 and entitled "Clinical Study on the Intensive Chemotherapy for Childhood Acute Lymphoblastic Leukemia." The document, relevant part of which has been translated into English, clearly indicates that CODPL is known in the art to represent "cyclophosphamide oncovin daunomycin prednione l-asparaginase." Applicant therefore respectfully requests withdrawal of this rejection.

III. Claim Rejections under 35 U.S.C. § 103(a)

A. *Yamabe and Okuda*

Claims 1 and 34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* ("*Yamabe*") in view of a journal publication by

Okuda *et al.* ("*Okuda*"). *See* Final Office Action at 5-8. The Office states that *Yamabe* teaches the preparation of riboflavin trilaurate but does not indicate the positions where any of the three laureates resides. *Id.* at 5. The Office, correctly declining to make an anticipation rejection over *Yamabe*, nonetheless took the position that "one of the esterified positions is the 5'-OH as it is the only primary alcohol on the riboflavin chain, as ... a primary alcohol reacts much faster than secondary alcohols." *Id.* at 5-6.

In an attempt to cure the defects of *Yamabe*, the Office states that *Okuda* teaches that (1) riboflavin tetrabutyrate had the same vitamin B2 activity as riboflavin, (2) riboflavin 5'-monobutyrate had the same vitamin B2 activity as riboflavin, (3) riboflavin tetrapalmitate did not have vitamin B2 activity, and (4) riboflavin 5'-monopalmitate had lower vitamin B2 activity compared to riboflavin 5'-monobutyrate. Those teachings led the Office to generalize that (1) for longer chain riboflavin ester compounds, riboflavin monoesters are better hydrolyzed than tetraesters and hence exhibit better vitamin B2 activity, and (2) shorter chain riboflavin esters are better hydrolyzed than longer ones and hence exhibit better vitamin B2 activity. The Office further reasons that (1) since monoesters are better hydrolyzed, one would have been motivated to modify the riboflavin trilaurate compound taught by *Yamabe* to riboflavin 5'-laurate, and (2) since shorter chain riboflavin esters are better hydrolyzed, one would also have been motivated to shorten the palmityl chain as taught by *Okuda* to a lauryl chain. *See* Final Office Action at 6-7. The Office therefore concludes that the inventions of claims 1 and 34 would have been obvious.

Continuing to disagree, Applicant respectfully submits that the Office has not established a prima *facie case* of obviousness.

1. The Rejection Contradicts the USPTO Guidelines Concerning Obviousness and Recent Federal Circuit Law and USPTO Law Regarding Obviousness.

In the chemical arts, a *prima facie* case of obviousness generally begins with a reasoned identification of a "**lead**" compound or compounds. *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.,* 533 F.3d 1353, 1359 (Fed. Cir. 2008); *Daiichi Sankyo Co. v. Matrix Laboratories Ltd.*, 619 F.3d 1346, 1352 (Fed. Cir. 2010) (citations omitted). "Structural similarity" alone is not enough to establish a *prima facie* case of obviousness *Eisai,* 533 F.3d at 1357; *Daiichi*, 619 F.3d at 1354. Rather, the Office must show (**1**) "motivation that would have led one of ordinary skill in the art to select" a lead compound; (**2**) the motivation for one skilled in the art to "then modify a known compound (i.e. a lead compound) in a particular way to achieve" the claimed compound; and (**3**) an expectation, "in light of the totality of the prior art, that the new compound will have similar properties to the [lead compound]." *Eisai*, 533 F.3d at 1357; *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-63 (Fed. Cir. 2007); *Daiichi*, 619 F.3d at 1352. *See also* the Office's discussion of *Eisai* and *Takeda* in 75 Fed. Reg. 53643, 53660 (Sept. 1, 2010) ("PTO Guidelines Concerning Obviousness").

A "lead" compound is one "that would be **most promising** to modify in order to improve upon its [desired] activity and obtain a compound with **better** activity." *Takeda*, 492 F.3d at 1357 (emphasis added). To be sure, it is not required that there be only one lead compound in the prior art. *Altana Pharma* v. *Teva*, 566 F.3d 999, 1008 (Fed. Cir. 2009). *See also* the Office's discussion of *Altana* in PTO Guidelines Concerning Obviousness, 75 Fed. Reg. at 53652-53653. But, the selection of a lead compound

"must avoid hindsight bias" and must focus on "the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention." *See Daiichi*, 619 F.3d at 1354 (emphasis original).

One of ordinary skill would not have selected a compound as a lead simply because it is structurally more close to the claimed compound, especially when there were other compounds having "**more favorable characteristics**." *See Id.* (emphasis added); *Takeda*, 492 F.3d at 1357-59. As such, "providing a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds." *Daiichi*, 619 F.3d at 1354.

Applicant respectfully submits that in this case the Office has failed to provide reasoning for identifying any compound in *Yamabe* or *Okuda* a "lead" compound.

2. The Office Has Failed to Establish a "Lead" Compound from Which to Begin an Obviousness Analysis.

Here, it appears that the Office has postulated **two "lead" compounds** to arrive at the claimed inventions: (**1**) riboflavin trilaurate of *Yamabe*, which allegedly can be modified to obtain a 5'-laurate, or (**2**) riboflavin 5'-palmitate of *Okuda*, which allegedly can be shortened to obtain a 5'-laurate. As detailed below, a person of ordinary skill in the art would not have picked those two compounds as leads for further modifications to achieve better vitamin B2 activity, but would have chosen for further research in improving the vitamin B2 activity of other more favorable compounds such as riboflavin 5'-butyrate, riboflavin tetrabutyrate, and riboflavin triisovalerate as leads.

More specifically, one of ordinary skill in the art would not have picked riboflavin trilaurate or riboflavin 5'-palmitate as a lead compound at the time of invention. *Okuda*

teaches that the vitamin B2 activity of riboflavin 5'-palmitate is "clearly lower" than that of riboflavin 5'-butyrate, and that riboflavin tetrapalmitate has no vitamin B2 activity. Hence, there is no rationale of record for picking riboflavin 5'-palmitate as a lead compound.

Regarding riboflavin trilaurate (having a **C12** chain), that compound is structurally more close to riboflavin 5'-palmitate or tetrapalmitate (having a **C16** chain) than to riboflavin 5'-butyrate (having a **C4** chain). Hence, a person of ordinary skill would have expected that riboflavin trilaurate either has no vitamin B2 activity, or has lower vitamin B2 activity than riboflavin 5'-butyrate.

Thus, one of ordinary skill would not have picked either of those two compounds as leads, because neither of them is a compound "with more favorable characteristics." *See Daiichi*, 619 F.3d at 1354; *Takeda*, 492 F.3d at 1357-59. The only basis for so picking is hindsight, which is inappropriate. *See Ex Parte Subramanyam*, 2010 WL 1253713 at 3-4 (BPAI, March 29, 2010).

And, if a person of ordinary skill were to have picked lead compounds from *Yamabe* and *Okuda*, s/he would have picked riboflavin 5'-butyrate or tetrabutyrate as a lead compound. *Okuda* teaches that both riboflavin 5'-butyrate and riboflavin tetrabutyrate had the same vitamin B2 activity as riboflavin itself, and that both riboflavin 5'-butyrate and riboflavin tetrabutyrate had better activity than riboflavin 5'-palmitate or tetrapalmitate. Since riboflavin 5'-butyrate and riboflavin tetrabutyrate were the "**most promising**" compounds at the time of the invention, one of ordinary skill would have picked them as leads for further modification. *See Takeda*, 492 F.3d at 1357 (emphasis

added); the Office's discussion of *Takeda* in PTO Guidelines Concerning Obviousness, 75 Fed. Reg. at 53654.

Alternatively, a person of ordinary skill may have picked riboflavin triisovalerate of *Yamabe* as a lead compound. *Yamabe* does not teach the relative activity of riboflavin trilaurate in comparison to riboflavin triisovalerate. But according to the Examiner's theory, shorter chain riboflavin esters are more easily hydrolyzed and thus have better activity than longer chain esters. A person of ordinary skill would thus have picked riboflavin triisovalerate (having a **C5** chain) as a lead compound rather than trilaurate because riboflavin triisovalerate has a much shorter chain than trilaurate, and is structurally more close to riboflavin 5'-butyrate and riboflavin tetrabutyrate.

For at least the reasons above, applicant respectfully submits that the Office has not provided any logical reason why riboflavin trilaurate or riboflavin 5'-palmitate should have been picked as lead compounds over other compounds that appear in the *Yamabe* and *Okuda* documents to have provided better leads for further modification to achieve better vitamin B2 activities. And for at least these reasons, the Office has not established a *prima facie* case of obviousness, and the rejection should be withdrawn.

B. *Yamabe, Okuda, Remington, the '740 patent, and Wicks*

Claims 6, 12, 23-26, 29, and 30 are rejected under 35 U.S.C. §103(a) as being unpatentable over *Yamabe*, in view of *Okuda* as applied to claims 1 and 34, further in view of Remington, The Science and Practice of Pharmacy ("*Remington*"), in view of U.S. Patent No. 6,245,740 to Goldenberg *et al.* ("the '740 patent"), and in view of PG Pub No. US 2002/0142972 to Wicks *et al.* ("*Wicks*"). *See* Final Office Action at 11-15. Applicant continues to disagree.

As discussed above, claims 1 and 34 are not obvious over *Yamabe* and *Okuda*. The secondary references cited do not cure the deficiencies of *Yamabe* and *Okuda*. Therefore, Applicant respectfully requests withdrawal of this rejection.

C. Yamabe, Okuda, Remington, the '740 patent, Wicks, and the '650 patent

Claims 7, 8, and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Yamabe*, in view of *Okuda* as applied to claims 1 and 34 above, further in view of *Remington*, the '740 patent, and *Wicks*, as applied to claims 6, 12, 23-26, 29, and 30, further in view of U.S. Patent No., 5,554,650 to Holl *et al.* ("the '650 patent"). Final Office Action at 15-19.

As discussed above, claims 1 and 34 are not obvious over *Yamabe* and *Okuda*. The secondary references cited do not cure the deficiencies of *Yamabe* and *Okuda*. Therefore, Applicant respectfully requests withdrawal of this rejection.

D. Yamabe, Okuda, Remington, the '740 patent, Wicks, Burzynski, and McCarthy

Claims 21, 22, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Yamabe* in view of *Okuda* as applied to claims 1 and 34 above, further in view of *Remington*, the '740 patent, and *Wicks*, as applied to claims 6, 12, 23-26, 29, and 30, further in view of PG Pub No. US 2003/0105104 A1 by Burzynski ("*Burzynski*"), in view of journal publication by McCarthy *et al.* ("*McCarthy*"). *See* Final Office Action at 20-23.

As discussed above, claims 1 and 34 are not obvious over *Yamabe* and *Okuda*. The secondary references cited do not cure the deficiencies of *Yamabe* and *Okuda*. Therefore, Applicant respectfully requests withdrawal of this rejection.

E. Yamabe, Okuda, Remington, the '740 patent, Wicks, and the '891 patent

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Yamabe* in view of *Okuda* as applied to claims 1 and 34 above, further in view of *Remington*, the '740 patent, and *Wicks*, as applied to 6, 12, 23-26, 29, and 30, further in view of U.S. Patent No. 6,565,891 to Chandra (" the '891 patent). *See* Final Office Action at 24-26.

As discussed above, claims 1 and 34 are not obvious over *Yamabe* and *Okuda*. The secondary references cited do not cure the deficiencies of *Yamabe* and *Okuda*. Therefore, Applicant respectfully requests withdrawal of this rejection.

IV. Conclusion

In view of the foregoing remarks, Applicant respectfully requests reconsideration of this application and timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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